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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/680,284	10/06/2000	Sigrid Lise Fossheim	REF/FOSSHEIM/100	8494

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EXAMINER

WELLS, LAUREN Q

ART UNIT	PAPER NUMBER
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1617

DATE MAILED: 02/13/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/680,284

Applicant(s)

FOSSHEIM ET AL.

Examiner

Lauren Q Wells

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 13 December 2001.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-13 and 23-38 is/are pending in the application.
- 4a) Of the above claim(s) 7 and 8 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-6,9-13 and 23-38 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 2. 6) ☐ Other:

DETAILED ACTION

Claims 1-13 and 23-38 are pending. Claims 7-8 are withdrawn from consideration as they are directed to non-elected subject matter. The Amendment received January 14, 2002 amended claims 10 and 12, cancelled claims 14-21 and added claims 24-38.

Election/Restrictions

An Election of Species was made in Paper No. 7, received January 14, 2002, without traverse. The election of species requirement is hereby made final.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 2, 6, 9 and 12-13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

(i) The phrase “contrast generating species” in claims 1 (line 5) is vague and indefinite, as it is not clear what compounds are encompassed by this phrase. This phrase is not defined in the specification and one of ordinary skill in the art would not be apprised of it. Is a contrast generating species a contrast agent? What species generate contrast?

(ii) The phrase “carbon dioxide tension” in claim 2 (line 3) is vague and indefinite, as it is not clear what type of measurement tension is. The specification does not define this phrase and one of ordinary skill in the art would not be apprised of it.

(iii) The phrase “tissue diffusion” in claim 2 (line 4) is vague and indefinite, as it is confusing. How do tissues diffuse? If all of our tissues diffused would we not be dead?

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(iv) Claim 6 is rejected for the use of improper Markush groups. See MPEP 2173.05(h) for examples of proper conventional or alternative Markush-type language (e.g., “. . .selected from the group consisting of. . .and . . .”).

(v) The phrase “in combination with” in claim 9 (line 2) is vague and indefinite, as it is not clear what this is referring to. Does it mean covalently bonded to the particulate material? Does it mean in composition with the particulate material?

(vi) The term "sensitive" in claim 12 (line 2) is a relative term which renders the claim indefinite. The term "sensitive" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

(vii) The terms "stable" and “normal” in claim 13 (lines 2 and 4) are relative terms which render the claim indefinite. The terms "stable" and “normal” are not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

(viii) The phrase “water permeability or leakage” in claim 13 (line 3) is vague and indefinite, as it is not clear how the phrases “permeable” and “leaking” are differentiated.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

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Claims 1-6, 9-13 and 23-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Unger (6,315,981) in view of Ozer et al. (Ep. Jn. Of Phar. And Biopharm.) or Sonek et al. (5,631,141) in further view of Unger (6,143,276).

Unger ('981) teach gas filled microspheres as MRI contrast agents, wherein the gaseous precursor is a compound which, at a selected activation or transition temperature, changes phases from a liquid to a gas. Activation thus takes place by increasing the temperature of the compound from a point below, to a point above the activation or transition temperature. The increase in temperature of the gaseous precursor can take place as a result of natural heating by the tissue or by external sources of energy, such as ultrasound. The microspheres are disclosed as mono or bilayer lipids, wherein phospholipids are preferred lipids. The gas filled microspheres are disclosed in a contrast medium which may include paramagnetic and/or superparamagnetic contrast agents, preferably encapsulated by the microspheres. Further disclosed is a method of imaging, wherein the contrast medium may comprise additional contrast agents, such as conventional contrast agents, serving to increase the efficacy of the contrast medium for MRI. Intravascular injection is disclosed as a mode of administration. The reference fails to exemplify the instant invention, fails to teach the matrix/membrane material as changing permeability or chemically or physically breaking down, and fails to teach a cell adhesion molecule. See Col. 4, line 65-Col. 6, line 6; Col. 13, line 1-Col. 15, line 52; Col. 20, line 12-Col. 23, line 12; Col. 28, line 34-Col. 30, line 20; Col. 36, line 23-Col. 39, line 67; Col. 45, line 24-Col. 48, line 65.

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Ozer et al. teach temperature and pH-sensitive liposomes, wherein the liposomes leak much more readily at the phase transition temperature of their membrane lipids. The liposomes are disclosed as enclosing drugs. See pg. 97-99.

Sonek et al. teach high resolution biosensors for in-situ microthermometry. The biosensor is disclosed as a vesicle comprising a phospholipid layer or bilayer. The vesicle is disclosed as being impregnated with a dopant that varies its optical emission spectrum as a function of the local environmental temperature of the biosensor. A method of measuring temperature is disclosed wherein the phase transition of the vesicle is measured. See Col. 2, line 28-line 60.

Unger ('276) teaches methods for delivering bioactive agents to regions of elevated temperatures and methods of imaging and diagnosing. Disclosed are compositions comprising bioactive agent, gaseous precursor and stabilizing material, wherein the stabilizing material can be in the form of a vesicle. Vesicles can be formulated with lipids and may also comprise targeting ligands. Bioactive agents can be diagnostic agents, such as contrast agents used in MRI and ultrasound imaging. The gaseous precursor is disclosed as being stabilized by biocompatible materials capable of forming a wall/membrane, such as phospholipids. At elevated temperatures the gaseous precursor forms a gas. The elevated temperature may be due to disease, infection, inflammation, or external heat, such as ultrasound. It is further disclosed that diagnostic ultrasound may be used in order to visualize the gaseous precursors as the gas is formed, and to visualize the tissue or region of interest. Parenteral administration is disclosed. MRI is disclosed as a mode of imaging. For imaging uses, a separately added diagnostic bioactive agent need not be employed with a gaseous precursor, but it can be added. See Col. 1, line 54-Col. 7, line

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12; Col. 8, line 66-Col. 9, line 60; Col. 11, line 25-Col. 14, line 28; Col. 37, line 32-Col. 43, line 7; Col. 48, line 9-Col. 52, line 24.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have exemplified a method of imaging comprising administering parenterally a particulate material comprising a matrix/membrane material and a contrast generating species, wherein the matrix/membrane material is responsive to a pre-selected physiological parameter whereby to alter the contrast efficacy of the species in response to a change in the value of the parameter; generating image data; and generating a signal indicative of the value/variation of the parameter using the teachings of Unger because a) Unger teaches a method of imaging comprising administering a gas filled microsphere, wherein the microsphere is a phospholipid membrane material and wherein the microsphere can encapsulate or be in composition with a paramagnetic contrast generating species; b) Unger teaches that an increase in temperature results in the gas undergoing a liquid-to-gas phase transition, wherein the microsphere enlarges in size, altering the magnetic domains of the environment.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use the teachings of Ozer et al. or Sonek et al. in the invention of Unger to teach the matrix/membrane material as responsive to a pre-selected physiological parameter because a) Unger, Ozer and Sonek all teach vesicles comprised of phospholipids that can encapsulate active agents; b) Unger and Ozer teach vesicles comprised of the same phospholipids; c) Ozer and Sonek teach their phospholipids as undergoing phase transitions under the influence of increased temperature; thus, since all three references teach vesicles comprising phospholipids and Unger and Ozer teach vesicles comprised of the same phospholipids, one would expect the vesicles of

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Unger to have similar properties; hence, teaching the phospholipids of Unger as responsive to increased temperature for imaging purposes would be within the skill of one in the art.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate the cell adhesion molecule of Unger ('276) in the particulate material of Unger ('981) because a) Unger and Unger both teach gas filled microspheres as imaging agents that undergo a liquid-to-gas phase transition under conditions of increased temperature; b) Unger (276) teaches that targeting ligands can be employed with gas filled microspheres to target specific regions of the body; hence, adding a targeting ligand to the gas filled microsphere composition of Unger('981) for imaging purposes would be within the skill of one in the art.

The claimed subject matter fails to patentably distinguish over the state of the art as represented by the cited references. Therefore, the claims are properly rejected under 35 U.S.C. § 103.

Prior Art

The prior art made of record and not specifically relied upon in any rejections cited above is either 1) considered cumulative to the prior art that was cited in a rejection or is 2) considered pertinent to the applicant's disclosure and shows the state of the art in its field but is not determined by the Examiner to read upon the invention currently being prosecuted in this application.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lauren Q Wells whose telephone number is (703) 305-1878. The examiner can normally be reached on T-F (6-4:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Minna Moezie can be reached on (703) 308-4612. The fax phone numbers for the

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organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1234.

lqw
January 31, 2002



DAMERON L. JONES
PRIMARY EXAMINER